S. Laureys (Ed.)
Progress in Brain Research, Vol. 150
ISSN 0079-6123

CHAPTER 34

The locked-in syndrome : what is it like to be conscious but paralyzed and voiceless?

Steven Laureys[1,*], Frédéric Pellas[2], Philippe Van Eeckhout[3], Sofiane Ghorbel[2], Caroline Schnakers[1], Fabien Perrin[4], Jacques Berré[5], Marie-Elisabeth Faymonville[6], Karl-Heinz Pantke[7], Francois Damas[8], Maurice Lamy[6], Gustave Moonen[1] and Serge Goldman[9]

[1]*Neurology Department and Cyclotron Research Center, University of Liège, Sart Tilman B30, 4000 Liege, Belgium*
[2]*Neurorehabilitation Medicine, Hôpital Caremeau, CHU Nîmes, 30029 Nîmes Cedex, France*
[3]*Department of Speech Therapy, Hospital Pitié Salpétrière, Paris and French Association Locked in Syndrome (ALIS), 225 Bd Jean-Jaures, MBE 182, 92100 Boulogne-Billancourt, France*
[4]*Neurosciences et Systèmes Sensoriels Unité Mixte de Recherche 5020, Université Claude Bernard Lyon 1 – CNRS, 69007 Lyon, France*
[5]*Intensive Care Medicine, Hôpital Erasme, Université Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium*
[6]*Anesthesiology, Reanimation and Pain Clinic, CHU University Hospital, Sart Tilman B33, 4000 Liege, Belgium*
[7]*German Association Locked in Syndrome LIS e.V., Evangelischen Krankenhaus Köningin Elisabeth Herzberge gGmbh (Lehrkrankenhaus der Charité), Haus 30, Herzbergstrasse 79, 10365 Berlin, Germany*
[8]*Intensive Care Medicine, Centre Hospitalier Régional de la Citadelle, Boulevard du 12e de Ligne 1, 4000 Liege, Belgium*
[9]*Biomedical PET Unit, Hôpital Erasme, Université Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium*

Abstract: The locked-in syndrome (pseudocoma) describes patients who are awake and conscious but selectively deefferented, i.e., have no means of producing speech, limb or facial movements. Acute ventral pontine lesions are its most common cause. People with such brainstem lesions often remain comatose for some days or weeks, needing artificial respiration and then gradually wake up, but remaining paralyzed and voiceless, superficially resembling patients in a vegetative state or akinetic mutism. In acute locked-in syndrome (LIS), eye-coded communication and evaluation of cognitive and emotional functioning is very limited because vigilance is fluctuating and eye movements may be inconsistent, very small, and easily exhausted. It has been shown that more than half of the time it is the family and not the physician who first realized that the patient was aware. Distressingly, recent studies reported that the diagnosis of LIS on average takes over 2.5 months. In some cases it took 4–6 years before aware and sensitive patients, locked in an immobile body, were recognized as being conscious. Once a LIS patient becomes medically stable, and given appropriate medical care, life expectancy increases to several decades. Even if the chances of good motor recovery are very limited, existing eye-controlled, computer-based communication technology currently allow the patient to control his environment, use a word processor coupled to a speech synthesizer, and access the worldwide net. Healthy individuals and medical professionals sometimes assume that the quality of life of an LIS patient is so poor that it is not worth living. On the contrary, chronic LIS patients typically self-report meaningful quality of life and their demand for euthanasia is surprisingly infrequent. Biased clinicians might provide less aggressive medical treatment and influence the family in inappropriate ways. It

*Corresponding author. Tel.: +32 4 366 23 16; Fax: +32 4 366 29 46; E-mail: steven.laureys@ulg.ac.be

DOI: 10.1016/S0079-6123(05)50034-7

is important to stress that only the medically stabilized, informed LIS patient is competent to consent to or refuse life-sustaining treatment. Patients suffering from LIS should not be denied the right to die — and to die with dignity — but also, and more importantly, they should not be denied the right to live — and to live with dignity and the best possible revalidation, and pain and symptom management. In our opinion, there is an urgent need for a renewed ethical and medicolegal framework for our care of locked-in patients.

> "*Io non mori', e non rimasi vivo*;
> *Pensa omai per te, s'hai fior d'ingegno,*
> *Qual io divenni, d'uno e d'altro privo*.
>
> *Neither did I die, nor did I remain alive*;
> *Imagine yourself, if your spirit is fine*,
> *what I came to be, deprived of both*."
>
> Alighieri Dante, 1265-1321, Divina Comedia, *Inferno* XXXIV, 25–27

> "*An old laborer, bent double with age and toil, was gathering sticks in a forest*.
> *At last he grew so tired and hopeless that he threw down the bundle of sticks, and cried out*:
> "*I cannot bear this life any longer. Ah, I wish Death would only come and take me!*"
> *As he spoke, Death, a grisly skeleton, appeared and said to him*:
> "*What wouldst thou, Mortal? I heard thee call me*."
> "*Please, sir*," *replied the woodcutter*,
> "*would you kindly help me to lift this faggot of sticks on to my shoulder*?"
>
> Aesop, approximately 620–560 B.C., The Old Man and Death (translated in verse by Jean de La Fontaine, 1621–1695, La Mort et le Bucheron) (Fig. 1).

It is hard to think of a physical disability more cruel than the inability to speak and to move the extremities. In 1966, Plum and Posner first introduced the term "locked-in syndrome" (LIS) to refer to the constellation of quadriplegia and anarthria brought about by the disruption of the brain stem's corticospinal and corticobulbar pathways, respectively (Plum and Posner, 1983). The earliest example of a "locked-in" patient in the medical literature comes from Darolles (1875). However, the locked-in syndrome was already brilliantly described 30 years earlier in Alexandre Dumas's novel *The Count of Monte Cristo* (1844–45) Dumas (1997, Original publication 1854). Herein a character, Monsieur Noirtier de Villefort, was depicted as "a corpse with living eyes." Mr. Noirtier had been in this state for more than 6 years, and he could only communicate by blinking his eyes. His helper pointed at words in a dictionary and the monsignor indicated with his eyes the words he wanted.

Some years later, Emile Zola wrote in his novel *Thérèse Raquin* (Zola, 1979, Original publication

Fig. 1. The Old Man and Death, artist unknown.

1868) about a paralyzed woman who "was buried alive in a dead body" and "had language only in her eyes." Dumas and Zola highlighted the locked-in condition before the medical community did. In the LIS, unlike coma, the vegetative state or akinetic mutism, consciousness remains intact. The patient is locked inside his body, able to perceive his environment but extremely limited to voluntarily interact with it. Both characters lived in an age when their ventral pontine lesion, which is most often vascular, should have killed them quickly. Indeed, for a long time, LIS has mainly been a retrospective diagnosis based on post-mortem findings (Haig et al., 1986; Patterson and Grabois, 1986). Medical technology can now achieve long survival in such cases — the longest history of this condition being 27 years (French Association of Locked-In Syndrome (ALIS)-database and Thadani et al., 1991). Computerized devices now allow the LIS patient and other patients with severe motor impairment to "speak." The preeminent physicist Stephen Hawking, author of the best sellers *A Brief History of Time* and *The Universe in a Nutshell*, is able to communicate solely through the use of a computerized voice synthesizer. With one finger, he selects words presentedserially on a computer screen; the words are then stored and later presented as a synthesized and coherent message (http://www.hawking.org.uk). The continuing brilliant productivity of Hawking despite his failure to move or speak illustrates that locked-in patients can be productive members of the society.

In December 1995, Jean-Dominique Bauby, aged 43 and editor in chief of the fashion magazine *Elle*, had a brain stem stroke. He emerged from a coma several weeks later to find himself in a LIS only able to move his left eyelid and with very little hope of recovery. Bauby wanted to show the world that this pathology, which impedes movement and speech, does not prevent patients from living. He has proven it in an extraordinary book (Bauby, 1997) in which he composed each passage mentally and then dictated it, letter by letter, to an amanuensis who painstakingly recited a frequency-ordered alphabet until Bauby chose a letter by blinking his left eyelid once to signify "yes". His book "The diving bell and the butterfly" became a best-seller only weeks after his death due to septic shock on March 9, 1997. Bauby created ALIS aimed to help patients with this condition and their families (www.club-internet.fr/alis).

Since its creation in 1997, ALIS has registered 367 locked-in patients in France (data updated in August 2004). What follows is a review of LIS, discussing studies on the cause, outcome, symptoms, and quality of life of locked-in patients based on the available literature and the ALIS database, which is the largest in its kind. The latter data should be regarded as a preliminary record of ongoing research. After elimination of patients with missing data, 250 patients were included for further analyses.

Classical, incomplete and total locked-in syndrome

Plum and Posner (1983) described the LIS as

> "a state in which selective supranuclear motor de-efferentation produces paralysis of all four limbs and the last cranial nerves without interfering with consciousness. The voluntary motor *paralysis* prevents the subjects from communicating by word or body movement. Usually, but not always, the anatomy of the responsible lesion in the brainstem is such that locked-in patients are left with the capacity to use vertical eye movements and blinking to communicate their awareness of internal and external stimuli."

Bauer et al. (1979) subdivided the syndrome on the basis of the extent of motor impairment: (a) *classical* LIS is characterized by total immobility except for vertical eye movements or blinking; (b) *incomplete* LIS permits remnants of voluntary motion; and (c) *total* LIS consists of complete immobility including all eye movements combined with preserved consciousness. The American Congress of Rehabilitation Medicine (1995) most recently defined LIS by (i) the presence of sustained eye opening (bilateral ptosis should be ruled out as a complicating factor); (ii) preserved basic cognitive abilities; (iii) aphonia or severe hypophonia;

(iv) quadriplegia or quadriparesis; and (v) a primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid.

Etiology

LIS is most frequently caused by a bilateral ventral pontine lesion (e.g., Plum and Posner, 1983, Patterson and Grabois, 1986) (Fig. 2A). In rarer instances, it can be the result of a mesencephalic lesion (e.g., Chia, 1991; Meienberg et al., 1979, Bauer et al., 1979). The most common etiology of LIS is vascular pathology, either a basilar artery occlusion or a pontine hemorrhage (see Table 1). Another relatively frequent cause is traumatic brain injury (Britt et al., 1977; Landrieu et al., 1984; Keane, 1986; Rae-Grant et al., 1989; Fitzgerald et al., 1997; Golubovic et al., 2004). Following trauma, LIS may be caused either directly by brain stem lesions, secondary to vertebral artery damage and vertebrobasilar arterial occlusion, or due to compression of the cerebral peduncles from tentorial herniation (Keane, 1986). It has also been reported secondary to subarachnoid hemorrhage and vascular spasm of the basilar artery (Landi et al., 1994), a brain stem tumor (Cherington et al., 1976; Hawkes and Bryan-Smyth, 1976; Pogacar et al., 1983; Inci and Ozgen, 2003; Breen and Hannon, 2004), central pontine myelinolysis (Messert et al., 1979; Oda et al., 1984; Morlan et al., 1990; Lilje et al., 2002), encephalitis (Pecket et al., 1982; Katz et al., 1992; Acharya et al., 2001), pontine abscess (Murphy et al., 1979), brain stem drug toxicity (Davis et al., 1972; Durrani and Winnie, 1991; Kleinschmidt-DeMasters and Yeh, 1992), vaccine reaction (Katz et al., 1992), and prolonged hypoglycemia (Negreiros dos Anjos, 1984; Mikhailidis et al., 1985).

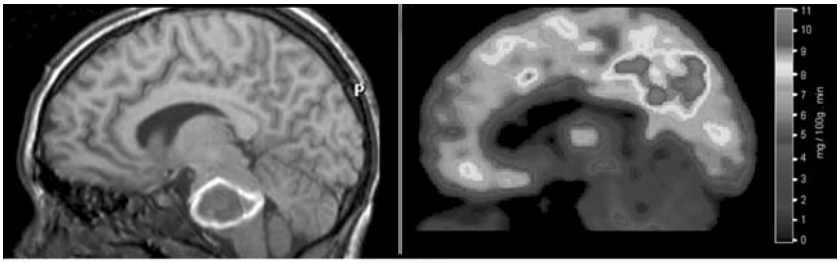

Fig. 2. (A) Magnetic resonance image (sagittal section) showing a massive hemorrhage in the brainstem (circular hyperintensity) causing a locked-in syndrome in a 13 year-old girl. (B) ^{18}F-fluorodeoxyglucose — Positron emission tomography illustrating intact cerebral metabolism in the acute phase of the LIS when eye-coded communication was difficult due to fluctuating vigilance. The color scale shows the amount of glucose metabolized per 100 g of brain tissue per minute. Statistical analysis revealed that metabolism in the supratentorial gray matter was not significantly lower as compared to healthy controls (Adapted from Laureys et al., 2004a). See Plate 34.2 in Color Plate Section.

Table 1. Etiology of the locked-in syndrome most frequently is vascular

Reference	Number of patients	(%) of males	Mean age at onset of LIS (range)	Vascular etiology (%)
Patterson and Grabois, (1986)	139	62	52 (20–77)	60
Katz et al. (1992)	29	66	34 (1–70)	52
Richard et al. (1995)	11	82	(17–73)	91
Casanova et al. (2003)	14	64	45 (16–71)	79
Leon–Carrion et al. (2002b)	44[a]	51	47 (22–77)	86
Pantke et al. (unpublished)	15	33	39	100
ALIS database	250	64	45 (13–84)	86

[a]These patients are part of the ALIS database.

A comparable awake conscious state simulating unresponsiveness may also occur in severe cases of peripheral polyneuropathy as a result of total paralysis of limb, bulbar, and ocular musculature. Transient LIS cases have been reported after Guillain Barré polyradiculoneuropathy (Loeb et al., 1984; Bakshi et al., 1997; Ragazzoni et al., 2000) and severe postinfectious polyneuropathy (Carroll and Mastaglia, 1979; O'Donnell, 1979). Unlike basilar artery stroke, vertical eye movements are not selectively spared in these extensive peripheral disconnection syndromes. Another important cause of complete LIS can be observed in end-stage amyotrophic lateral sclerosis, i.e., motor-neuron disease (Hayashi and Kato, 1989; Kennedy and Bakay, 1998; Kotchoubey et al., 2003). Finally, temporary pharmacologically induced LIS can sporadically be observed in general anesthesia when patients receive muscle relaxants together with inadequate amounts of anesthetic drugs (e.g., Sandin et al., 2000). Testimonies from victims relate that the worst aspect of the experience was the anxious desire to move or speak while being unable to do so (Anonymous, 1973; Brighouse and Norman, 1992; Peduto et al., 1994). Awake–paralyzed patients undergoing surgery may develop posttraumatic stress disorder (for recent review see Sigalovsky, 2003).

Misdiagnosis

Unless the physician is familiar with the signs and symptoms of the LIS, the diagnosis may be missed and the patient may erroneously be considered as being in a coma, vegetative state, or akinetic mustism (Gallo and Fontanarosa, 1989). In a recent survey of 44 LIS patients belonging to ALIS, the first person to realize the patient was conscious and could communicate via eye movements most often was a family member (55% of cases) and not the treating physician (23% of cases) (Table 2) (Leon-Carrion et al., 2002b). Most distressingly, the time elapsed between brain insult and LIS diagnosis was on average 2.5 months (78 days). Several patients were not diagnosed for more than 4 years. Leon-Carrion et al. (2002b) believed that this delay in the diagnosis of LIS mainly reflected initial misdiagnosis. Clinical experience indeed shows how difficult it is to recognize unambiguous signs of conscious perception of the environment and of the self in severely brain-injured patients (for review see Majerus et al., this volume). Voluntary eye movements and/or blinking can erroneously be interpreted as reflexive in anarthric and nearly completely paralyzed patients who classically show decerebration posturing (i.e., stereotyped extension reflexes). However, part of the delay could be explained by an initial lower level neurological state (e.g., decreased or fluctuating arousal levels) or even psychiatric symptoms that would mask residual cognitive functions at the outset of LIS.

Table 2. First person to realize the patient was conscious and could communicate via eye movements in 44 LIS patients. From an ALIS survey by Leon–Carrion et al. (2002)

Person making diagnosis	Number of patients (% of total)
Family member	24 (55)
Physician	10 (23)
Nurse	8 (18)
Other	2 (4)

Some memoirs written by LIS patients well illustrate the clinical challenge of recognizing a LIS. A striking example is *Look Up for Yes* written by Julia Tavalaro (1997). In 1966, 32-year old Tavalaro fell into a coma following a subarachnoid hemorrhage. She remained comatose for 7 months and gradually woke up to find herself in a New York State chronic care facility. There, she was known as "the vegetable" and it was not until 1973 (i.e., after 6 years) that her family identified a voluntary "attempt to smile" when Julia was told a dirty joke. This made speech therapist Arlene Kraat brake through Julia's isolation. With the speech therapist pointing to each letter on a letter board, Julia began to use her eyes to spell out her thoughts and relate the turmoil of her terrible years in captivity. She later used a communication device, started to write poetry and could cheek-control her wheelchair around the hospital. Julia Tavalaro died in 2003 at the age of 68 from aspiration pneumonia.

Another poignant testimony comes from Philippe Vigand, author of *Only the Eyes Say Yes*

(Vigand and Vigand, 2000, original publication in 1997) and formerly publishing executive with the French conglomerate, Hachette. The book is written in two parts: the first by Philippe, and the second by his wife Stéphane detailing *her* experiences. In 1990, Philippe Vigand, 32-years old, presented a vertebral artery dissection and remained in a coma for 2 months. Philippe and his wife write that at first, doctors believed he was a "vegetable and was treated as such." His wife eventually realized that he was blinking his eyes in response to her comments and questions to him but had difficulties convincing the treating physicians. It was speech therapist Philippe Van Eeckhout who formally made the diagnosis of LIS: when testing Vigand's gag reflex, Van Eeckhout was bit in his finger and yelled "chameau" (French for 'camel'), whereupon the patient started to grin. On the subsequent question "how much is 2 plus 2" Vigand blinked four times confirming his cognitive capacities. He later communicated his fist phrase by means of a letter board: "my feet hurt." After many months of hospital care, Vigand was brought home, where an infrared camera attached to a computer enabled him to "speak." The couple conceived a child after Philippe became paralyzed and he has written his second book (dealing with the menaced French ecosystem) on the beach of the Martinique isles (Vigand, 2002), illustrating that LIS patients can resume a significant role in family and society.

Survival and mortality

It has been stated that long-term survival in LIS is rare (Ohry, 1990). Mortality is indeed high in acute LIS (76% for vascular cases and 41% for nonvascular cases) with 87% of the deaths occurring in the first 4 months (Patterson and Grabois, 1986). In 1987, Haig et al. (1987) first reported on the life expectancy of persons with LIS, showing that individuals can actually survive for significant periods of time. Encompassing 29 patients from a major US rehabilitation hospital who had been in LIS for more than 1 year, they reported formal survival curves at the fifth year (Katz et al., 1992) and follow-up at the 10th year (Doble et al., 2003). These authors have shown that once a patient has medically stabilized in LIS for more than a year, 10-year survival is 83% and 20 year-survival is 40% (Doble et al., 2003).

Data from the ALIS database ($n = 250$) show that survivors are younger at onset than those who die (survivor mean 45 ± 14 years, deceased subjects 56 ± 13 years, $p < 0.05$), but there is no significant correlation between age at onset and survival time (Fig. 3). The mean time spent locked-in is 6 ± 4 years (range 14 days to 27 years, the latter patient still being alive). Reported causes of death of the 42 subjects are predominantly infections (40%, most frequently pneumonia), primary brain stem stroke (25%), recurrent brain stem stroke (10%), patient's refusal of artificial nutrition, and hydration (10%), and other causes (i.e., cardiac arrest, gastrostomy-surgery, heart failure, and hepatitis). It should be noted that the ALIS database does not contain the many LIS patients who die in the acute setting without being reported to the association. Recruitment to the ALIS database is based on case-reporting by family and health care workers prompted by the exceptional media publicity of ALIS in France and tracked by continuing yearly surveys. This recruitment bias should, however, be taken into account when interpreting the presented data.

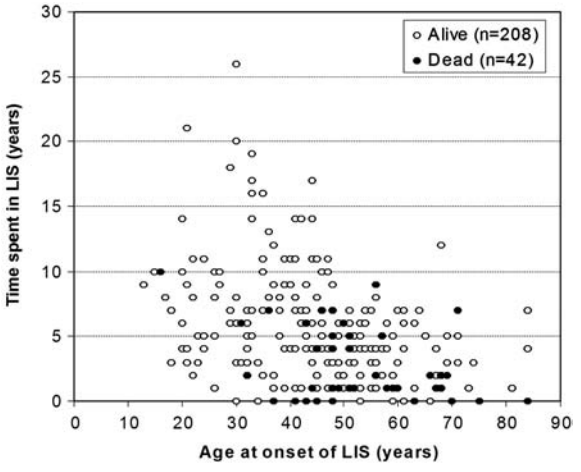

Fig. 3. Age at insult versus survival time of 250 locked-in patients registered in the ALIS (Association Locked in Syndrome) database, 42 of whom died (filled circles).

Prognosis and outcome

Classically, the motor recovery of LIS of vascular origin is very limited (Patterson and Grabois, 1986, Doble et al., 2003), even if rare cases of good recovery have been reported (McCusker et al., 1982; Ebinger et al., 1985). Chang and Morariu (1979) reported the first transient LIS caused by a traumatic damage of the brain stem. In their milestone paper, Patterson and Grabois (1986), reviewed 139 patients — 6 cases from the authors' rehabilitation center in Texas, USA, and 133 from 71 published studies from 1959 to 1983 — and reported earlier and more complete recovery in nonvascular LIS compared to vascular LIS. Return of horizontal pursuit eye movements within 4 weeks post-onset are thought to be predictive of good recovery (Chia, 1991). Richard et al. (1995) followed 11 LIS patients for 7 months to 10 years and observed that despite the persisting serious motor deficit, all patients did recover some distal control of fingers and toe movements, often allowing a functional use of a digital switch. The motor improvement occurred with a distal to proximal progression and included a striking axial hypotonia.

LIS is uncommon enough that many clinicians do not know how to approach rehabilitation and there are no existing guidelines as how to organize the revalidation process. Casanova et al. (2003) recently followed 14 LIS patients in 3 Italian rehabilitation centers for a period of 5 months to 6 years. They reported that intensive and early rehabilitative care improved functional outcome and reduced mortality rate when compared to the older studies by Patterson and Grabois (1986) and Katz et al. (1992). These results are in line with preliminary retrospective observations from the German Association for LIS lead by Pantke (2005).

Often unknown to physicians caring for LIS in the acute setting and despite the limited motor recovery of LIS patients, many patients can return living at home. The ALIS database shows that out of 245 patients, 108 (44%) are known to live at home (21% are staying in a hospital setting and 17% in a revalidation center). Patients return home after a mean period of 2 ± 16 years (range 2 months to 6 years, data obtained on $n = 55$). Results obtained in 95 patients show a moderate to significant recovery of head movement in 92% of patients, 65% showed small movement in one of the upper limbs (finger, hand, or arm), and 74% show a small movement in lower limbs (foot or leg). Half of the patients has recovered some speech production (limited to single comprehensible words) and 95% can vocalize unintelligible sounds (data obtained on $n = 50$). Some kind of electrical communication device is used by 81% of the LIS patients (data obtained on $n = 95$).

While all locked-in patients initially had a tracheotomy, 65% had it removed at the time of the last questionnaire. The mean interval to the removal of the tracheotomy was 14 ± 16 months (range 2 weeks to 5 years, data obtained on $n = 66$). All patients also initially had a gastrostomy and 58% had it removed at the time of the questionnaire; 66% of patients were able to have some kind of oral feeding (normal or mixed food, sometimes in addition to gastrostomy). The mean interval to removal of the gastrostomy was 18 ± 20 months (range 2 weeks to 6 years, data obtained on $n = 64$).

The level of care remains extensive in chronic LIS. Out of 50 questioned patients, 16 had nursing care once a day, 28 two times a day, and 6 three times a day. Physical therapy was performed at least five times a week in 66% of the patients, and speech therapy was performed at least three times a week in 55% of the patients. Nearly all patients (96%) complained of spasticity, 75% from difficulties swallowing oropharyngeal secretions, 66% from sialorrhea, and 61% had respiratory difficulties of various types.

Communication

In order to functionally communicate, it is necessary for the LIS patient to be motivated and to be able to receive (verbally or visually, i.e., written commands) and emit information. The first contact to be made with these patients is through a code using eyelid blinks or vertical eye movements. In cases of bilateral ptosis, the eyelids need to be manually opened in order to verify voluntary eye movements on command. To establish a yes/no

eye code, the following instruction can suffice : ''yes'' is indicated by one blink and ''no'' by two or look up indicates ''yes'' and look down ''no.'' In practice, the patient's best eye movement should be chosen and the same eye code should be used by all interlocutors. Such a code will only permit to communicate via closed questions (i.e., yes/no answers on presented questions). The principal aim of reeducation is to reestablish a genuine exchange with the LIS patient by putting into place various codes to permit them to reach a higher level of communication and thus to achieve an active participation. With sufficient practice, it is possible for LIS patients to communicate complex ideas in coded eye movements. Feldman (1971) first described a LIS patient who used jaw and eyelid movements to communicate in Morse Code.

Most frequently used are alphabetical communication systems. The simplest way is to list the alphabet and ask the LIS patient to make a prearranged eye movement to indicate a letter. Some patients prefer a listing of the letters sorted in function of appearance rate in usual language (i.e., in the French language: E—S—A—R—I—N—T—U—L—O—M—D—P—C—F—B—V—H—G—J—Q—Z—Y—X—K – W; or in the English language: E—T—A—O—I—N—S—R—H—L—D—C—U—M—F—P—G—W—Y—B—V—K—X—J—Q—Z). The interlocutor pronounces the letters beginning with the most frequently used, E, and continues until the patient blinks after hearing the desired letter, which the interlocutor then notes. It is necessary to begin over again for each letter to form words and phrases. The rapidity of this system depends upon practice and the ability of patient and interlocutor to work together. The interlocutor may be able to guess at a word or a phrase before all the letters have been pronounced. It is sufficient for him to pronounce the word or the rest of the sentence. The patient than confirms the word by making his eye code for ''yes'' or disproves by making his eye code for ''no.''

Another method is the ''vowel and consonant method.'' Here, the alphabet is divided into 4 groups : Vowels, Consonants 1 (B-H), Consonants 2 (J-Q), and Consonants 3 (R-Z) (Table 3). The interlocutor says : ''Vowel'' and then Consonants 1, 2, 3 and the patient blinks his eyelid to indicate the chosen group (Table 3).

A similar system is the ''alphabetical system using a grid of letters'' (Table 4). Here, to designate, for example, the letter ''B'' (1-1), the patient blinks his eye once, pauses, and then blinks one time again. If he wishes to designate a vowel, he raises his eyes before blinking. After using this system for a certain length of time, both the patient and the person communicating with the patient know it by heart. The patient indicates the position of the chosen letter with his eyes ; the interlocutor guesses the letter. The resulting dialogue can become remarkably rapid. There are many other variants

Table 3. Vowel and consonant method

V	C1	C2	C3
A	B	J	R
E	C	K	S
I	D	L	T
O	F	M	V
U	G	N	W
Y	H	P	X
		Q	Z

Notes: V, Vowel, C1,C2,C3 consonants. See text for details of use. From van Eeckhout (1997).

Table 4. Alphabetical system using a grid of letters

	Consonants	Consonants	Consonants	Consonants	Consonants	Vowels	Vowels
	1	2	3	4	5	1	2
1	B	G	L	Q	V	A	O
2	C	H	M	R	W	E	U
3	D	J	N	S	X	I	Y
4	F	K	P	T	Z		

Notes: See text for details of use. From van Eeckhout (1997).

to these systems which should be tailored to the patient's preferences and physical capabilities.

The above discussed systems all require assistance from others. It is important to stress that access to informatics is drastically changing the lives of patients with LIS. Instead of passively responding to the requests of others, computers allow the patient to initiate conversations and prepare detailed messages for caregivers who do not have time for lengthy guessing rounds. Experts in rehabilitation engineering and speech-language pathology device various patient-computer interfaces such as infra-red eye movement sensors (e.g., Quick Glance www.eyetechds.com or Eyegaze Communication System www.eyegaze.com/index-dis.htm) which can be coupled to on-screen virtual keyboards (e.g., WiViK www.wivik.com) allowing the LIS patient to control his environment (lights, appliances, etc.), use a word processor (which can be coupled to a text-to-speech synthesizer), operate a telephone or fax, or access the Internet and use e-mail (see Fig. 4). Unfortunately, the cost of these computer interfaces are often substantial and not routinely paid for by third parties.

Fig. 4. A locked-in person updates the database of ALIS, moving the cursor on screen by eye movements. An infrared camera (white arrow) mounted below the monitor observes one of the user's eyes, an image processing software continually analyzes the video image of the eye and determines where the user is looking on the screen. The user looks at a virtual keyboard that is displayed on the monitor and uses his eye as a computer-mouse. To "click" he looks at the key for a specified period of time (typically a fraction of a second) or blinks. An array of menu keys allow the user to control his environment, use a speech synthesizer, browse the worldwide web or send electronic mail independently (picture used with kind permission from DT). With a similar device Philippe Vigand, locked-in since 1990, has written a testimony of his LIS experience in an astonishing book *Putain de silence* (1997) translated as *Only the Eyes Say Yes* (2000). Photograph by S. Laureys.

Residual brain function

Neuropsychological testing

Surprisingly, there are no systematic neuropsychological studies of the cognitive functions in patients living with a LIS. Most case reports, however, failed to show any significant cognitive impairment when LIS patients were tested 1 year or more after the brainstem insult. Allain et al. (1998) performed extensive neuropsychological testing in two LIS patients studied 2 and 3 years after their basilar artery thrombosis. Patients communicated via a communication print–writer system and showed no impairment of language, memory and intellectual functioning. Cappa et al. (1985, 1982) studied one patient who was LIS for over 12 years and observed intact performances on language, calculation, spatial orientation, right–left discrimination and personality testing. Recently, New and Thomas (2005) assessed cognitive functioning in LIS patient 6 months after basilar artery occlusion, and noted significant reduction in speed of processing, moderate impairment of perceptual organization and executive skills, mild difficulties with attention, concentration, and new learning of verbal information. Interestingly, they subsequently observed progressive improvement in most areas of cognitive functioning until over 2 years after his brainstem stroke.

In a survey conducted by ALIS and Léon-Carrion et al. (2002b) in 44 chronic LIS patients, 86% reported a good attentional level, all but two patients could watch and follow a film on TV, and all but one were well-oriented in time (mean duration of LIS was 5 years). More recently, ALIS and Schnakers et al. (2005) adapted a standard battery of neuropsychological testing (i.e., sustained and selective attention, working and episodic memory, executive functioning, phonological and

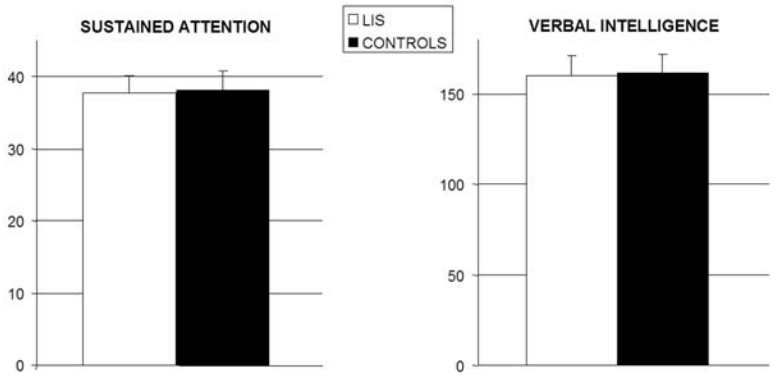

Fig. 5. Sustained attention, assessed by means of a newly developed auditory attention task, and verbal intelligence, assessed using the French adaptation of the Peabody Picture Vocabulary Test (Dunn and Thériault-Whalen, 1993), in five chronic LIS patients (three males; aged 24–57 years; LIS duration 3–6 years) and 10 healthy controls, matched for age, gender, and educational level. Data taken from Schnakers et al. (2005).

lexico-semantic processing, and vocabulary knowledge) to an eye-response mode for specific use in LIS patients. Overall, performances in the five LIS patients studied 3–6 years after their brainstem insult were not significantly different from 10 matched, healthy controls who, like the LIS patients, had to respond solely via eye-movements (Fig. 5). These data re-emphasize the fact that LIS due to purely pontine lesions is characterized by the restoration of a globally intact cognitive potential.

Electrophysiologic measurements

Markand (1976) reviewed electroencephalographic (EEG) recordings in eight patients with LIS and reported it was normal or minimally slow in seven and showed reactivity to external stimuli in all patients. These results were confirmed by Bassetti et al. (1994) who observed a predominance of reactive alpha activity in six LIS patients. In their seminal paper, Patterson and Grabois (1986) reported normal EEG findings in 39 (45%) and abnormal (mostly slowing over the temporal or frontal leads or more diffuse slowing) in 48 (55%) patients out of 87 reviewed patients. Jacome and Morilla-Pastor (1990), however, reported three patients with acute brainstem strokes and LIS whose repeated EEG recordings exhibited an ''alpha coma'' pattern (i.e. alpha rhythm unreactive to multimodal stimuli). Unreactive EEG in LIS was also reported by Gutling et al. (1996) confirming that lack of alpha reactivity is not a reliable indicator of unconsciousness and cannot be used to distinguish the ''locked-in'' patients from those comatose due to a brainstem lesion. Nevertheless, the presence of a relatively normal reactive EEG rhythm in a patient that appears to be unconscious should alert one to the possibility of a LIS.

Somatosensory-evoked potentials are known to be unreliable predictors of prognosis (Bassetti et al., 1994, Towle et al., 1989) but motor-evoked potentials have been proposed to evaluate the potential motor recovery (e.g., Bassetti et al., 1994).

Cognitive event-related potentials (ERPs) in patients with LIS may have a role in differential diagnosis of brainstem lesions (Onofrj et al., 1997) and have also shown their utility to document consciousness in total LIS due to end-stage amyotrophic lateral sclerosis (Kotchoubey et al., 2003) and fulminant Guillain–Barré syndrome (Ragazzoni et al., 2000). Fig. 6 shows event-related potentials in a 57-year-old locked-in patient following basilar artery thrombosis showing a positive ''P3'' component (peaking at 700 ms) only evoked by the patient's own name (thick line) and not by other names (thin line). It should, however, be noted that such responses can also be evoked in minimally conscious patients (Laureys et al., 2004b) and that they even persist in sleep in normal subjects (Perrin et al., 1999).

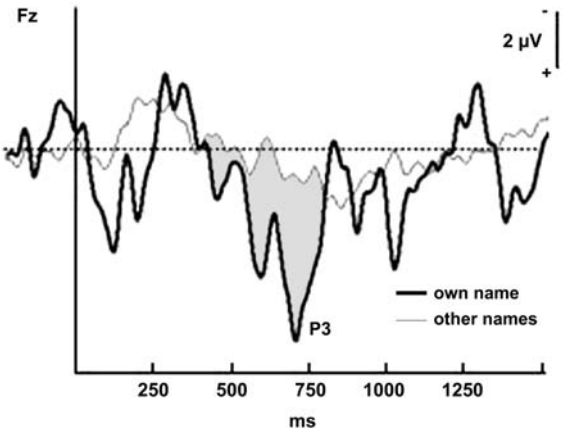

Fig. 6. Event-related potentials in chronic LIS. Patient JB (Adapted from Perrin et al., 2005).

Functional neuroimaging

Classically, structural brain imaging (MRI) may show isolated lesions (bilateral infarction, hemorrhage, or tumor) of the ventral portion of the basis pontis or midbrain (e.g., Leon-Carrion et al., 2002a). PET scanning has shown significantly higher metabolic levels in the brains of patients in a LIS compared to patients in the vegetative state (Levy et al., 1987). Preliminary results from ongoing PET studies by Laureys et al. (2003, 2004a) indicate that no supra-tentorial cortical area show significantly lower metabolism in acute and chronic LIS patients when compared to age-matched healthy controls (Fig. 2B). Conversely, a significantly hyperactivity was observed in bilateral amygdala of acute, but not in chronic, LIS patients. The absence of metabolic signs of reduced function in any area of the gray matter re-emphasizes the fact that LIS patients suffer from a pure motor de-efferentation and recover an entirely intact intellectual capacity. Previous PET studies in normal volunteers have demonstrated amygdala activation in relation to negative emotions such as fear and anxiety (e.g., Calder et al., 2001). It is difficult to make judgments about patient's thoughts and feelings when they awake from their coma in a motionless shell. However, in the absence of decreased neural activity in any cortical region, we assume that the increased activity in the amygdala in acute non-communicative LIS patients, relates to the terrifying situation of an intact awareness in a sensitive being, experiencing frustration, stress and anguish, locked in an immobile body. These preliminary findings emphasize the need for a quick diagnosis and recognition of the terrifying situation of a pseudocoma (i.e., LIS) at the intensive care or coma unit. Health care workers should adapt their bedside-behavior and consider pharmacological anxiolytic therapy of locked-in patients, taking into account the intense emotional state they go through.

Daily activities

For those not dealing with these patients on a daily basis it is surprising to see how chronic LIS patients, with the help of family and friends, still have essential social interaction and lead meaningful lives. Doble et al. (2003) reported that most of their chronic LIS patients continued to remain active through eye and facial movements. Listed activities included TV, radio, music, books on tape, visiting with family, visit vacation home, e-mail, telephone, teaching, movies, shows, the beach, bars, school, and vocational training. They also reported an attorney who uses Morse code eye blinks to provide legal opinions and keeps up with colleagues through fax and e-mail. Another patient taught math and spelling to third graders using a mouth stick to trigger an electronic voice device. The authors reported being impressed with the social interactions of chronic LIS patients and stated it was apparent that the patients were actively involved in family and personal decisions and that their presence was valued at home. Only four out of the 13 patients used computers consistently, two accessed the internet and one was able to complete the telephone interview by himself using a computer and voice synthesizer. A survey by ALIS and Ghorbel et al. (2002) showed that out of 17 questioned chronic LIS patients living at home, 11 (65%) used a personal computer.

Quality of life

In March 2002, at the annual meeting of ALIS at La Pitié-Salpétrière hospital in Paris, patients with LIS and their family members were asked to fill in the Short Form-36 (SF-36) questionnaire (Ware et al., 1993) on quality of life. Seventeen chronic (i.e., >1 year) locked-in patients who did not show major motor recovery (i.e., used eye movements or blinking as the major mode of communication) and who lived at home replied to the questionnaire (mean age 44 ± 6 years; range 33–57 years). Mean time of LIS duration was 6 ± 4 years (range 2–16 years). On the basis of the SF-36 questionnaire locked-in patients unsurprisingly showed maximal limitations in physical activities (all patients scoring zero). Interestingly, self-scored perception of mental health (evaluating mental well-being and psychological distress) and personal general health were not significantly lower than values from age-matched French control subjects (Fig. 7). Perception of mental health and the presence of physical pain was correlated to the frequency of suicidal thoughts ($r = -0.67$ and 0.56 respectively, $p < 0.05$). This stresses the importance (and current frequent inadequacy) of proper pain management in chronic LIS patients.

These findings confirm earlier reports on quality of life assessments in chronic locked-in patients. Previous surveys from ALIS ($n = 44$) showed that 48% regarded their mood as good versus 5% as bad; 13% declared being depressed; 73% enjoyed going out and 81% met with friends at least twice a month (Leon-Carrion et al., 2002b). In the study from Doble et al. (2003) 7 out of 13 patients were satisfied with life in general and 5 were occasionally depressed. As stated by Doble and co-workers, the results of studies on quality of life in chronic LIS may run contrary to many health care professionals. Superficially involved for the short term when the patient is at his or her worst, clinicians may often tend to comfortably assume that these persons will die anyway, or would choose to die if they only knew what the clinicians knew. As a result, debates about cost, daily management, quality of life, withdrawal or withholding of care,

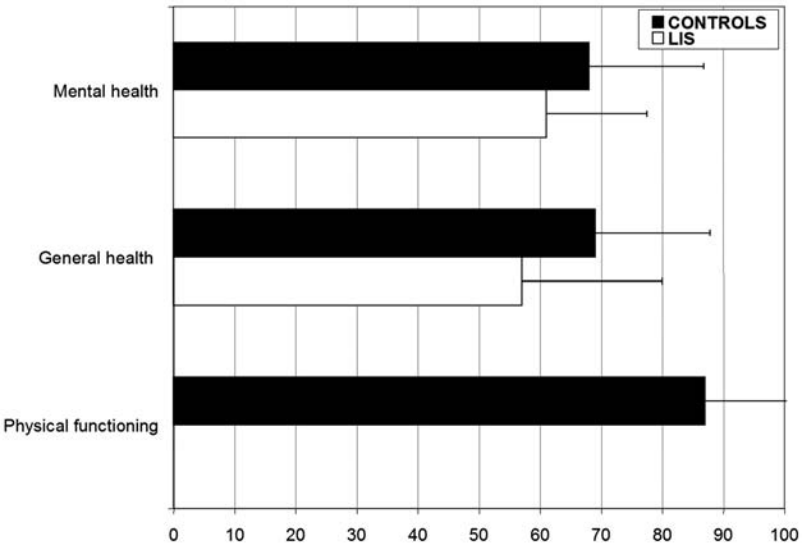

Fig. 7. Self-scored mental health, general health and physical functioning as assessed by a French version of the Short Form-36 (Ware et al., 1993) in 15 chronic locked-in patients living at home (white bars) compared to healthy age-matched French controls (black bars). Values are means and standard deviations. For all measures the reporting frame is the past month, scores range from 0 to 100, with higher scores representing better health-related quality of life. Note that physical functioning was scored as zero in all locked-in patients, but the perception of mental health (evaluating mental well-being and psychological distress) and personal general health were not significantly different in patients compared to healthy controls (historical control data taken from Leplege et al., 1998). Adapted from a survey conducted by ALIS and Ghorbel et al. (2002).

end-of-life decisions and euthanasia often go on with prejudice and without any input from the conscious but mute and immobile patient. To ''judge a book by its cover'' is unfair. Clinicians should realize that quality of life often equates with social rather than physical interaction and that the will to live is strong when struck by an acute devastating disease.

It is distressing to note that many people with disabilities feel their physicians will be too quick to help them with euthanasia (Batavia, 1997). Medical treatment for persons with LIS should be as aggressive as it would be for other people with potential survival of a decade or more. Contrary to the perceptions of some health care professionals who have not experienced such a severe motor disability, LIS patients typically have a wish to live. As discussed above, many return home and start a new, different, but meaningful life. In the future, more widely available access to enhanced communication computer prosthetics should additionally enhance the quality of life of locked-in patients.

The right to die or the right to live ?

The American Academy of Neurology (AAN) has published a position statement concerning the management of conscious and legally competent patients with profound and permanent paralysis (Ethics and Humanities Subcommittee of the AAN, 1993, Bernat et al., 1993, Allen, 1993). The conclusion is that such patients have the right to make health care decisions about themselves, including whether to accept or refuse life-sustaining therapy — either not start or stop once it started. Doctors caring for LIS have ''an ethical obligation to minimize subsequent suffering'' and should help patients with pain and dyspnea, ''even if these medications contribute… to respiratory depression, coma, or death.'' However, patients should first be fully informed about their condition and the treatment options and patients' decision must be consistent over a period of time. The latter is clearly necessary to exclude the impulsive transient reactions of despair that are common in patients with severe illness.

Since its creation in March 1997, ALIS has registered 367 patients with LIS in France. Four reported deaths were related to the patient's wish to die (unpublished data from ALIS' database). Doble et al. (2003) accounted that none of the 15 deaths of their study cohort of 29 chronic LIS patients from the Chicago area followed for over a decade could be attributed to euthanasia. None of their 13 chronic LIS patients had a ''do not resuscitate'' order, 7 had never considered or discussed euthanasia, 6 had considered it in the past but not at the time of survey and 1 wished to die.

In the survey conducted by ALIS and Ghorbel (2002) most of chronic LIS patients without motor recovery (i.e., worst-case scenario) rarely or never had suicidal thoughts (Fig. 8; mean age 45 years, mean duration of LIS 6 years). In reply to the question ''would you like to receive antibiotics in case of pneumonia ?'' 80% answered ''yes'' and to the question ''would you like reanimation to be tempted in case of cardiac arrest ?'' 62% answered positively. Anderson et al. (1993) reported suicidal thoughts in four out of seven LIS patients with long-term survival but all patients nevertheless wanted life-sustaining treatment (mean age 43 years, duration of LIS ranged from 8 to 37 months). Similarly, in the case of high spinal cord injury resulting in acute onset quadriplegia, Hall et al. (1999) reported that 81 out of 85 survivors surveyed (95%) were ''glad to be alive,'' including

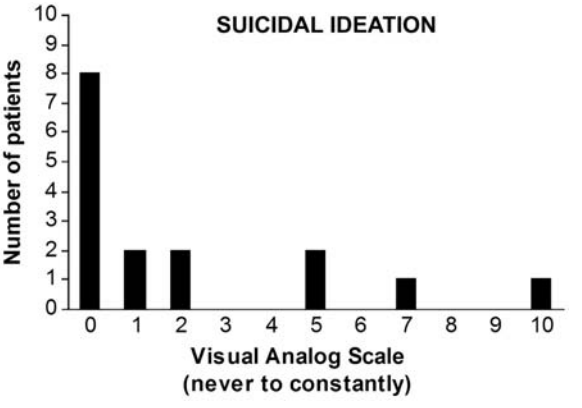

Fig. 8. Frequency of suicide thoughts in patients with chronic locked-in syndome. Note that 75% of the patients rarely or never had suicidal thoughts. From a survey conducted by ALIS and Ghorbel et al. (2002).

all ventilator-assisted patients studied 14 to 24 years post-trauma.

While the right of LIS individuals to withdraw from treatment is not questioned (Humbert, 2003, Guerra, 1999), the discussed data call into question the assumption among some health care workers and policy makers that severe disability is intolerable. The unfortunate consequence of this prejudice is that biased clinicians might provide less aggressive medical treatment and influence family in ways not appropriate to the situation (Doble et al., 2003). Likewise, in amyotrophic lateral sclerosis, ill-informed patients are regularly advised by physicians to refuse intubation and withhold life-saving interventions (Christakis and Asch, 1993, Trail et al., 2003). However, ventilator users with neuromuscular disease report meaningful life satisfaction (Kubler et al., 2005). Bach (2003) warns that ''virtually no patients are appropriately counseled about all therapeutic options'' and states that advance directives, although appropriate for patients with terminal cancer, are inappropriate for patients with severe motor disability.

Katz et al. (1992) cite the Hastings Center Report, ''Who speaks for the patient with LIS?.'' With the initial handicap of communicating only through eyeblink who can decide whether the patient is competent to consent or to refuse treatment (Steffen and Franklin, 1985)? With regard to end-of-life decisions taken in LIS patients, an illustrative case is reported by Fred (1986). His 80-year-old mother became locked-in. In concert with the attending physician, without consent of the patient herself, the decision was made to ''have her senses dulled'' and provide supportive care only. She died shortly thereafter with a temperature of 109°F (43°C). In the accompanying editorial, Stumpf (1986) commented that ''human life is to be preserved as long as there is consciousness and cognitive function in contrast to a vegetative state or neocortical death.''

Conclusion

The discussed data stress the need for heath care workers who might be confronted to the LIS to recognize this infrequent syndrome as early as possible and to adapt their bedside-behavior. Physicians who take care of acute LIS patients need a better understanding of their long-term outcome. With appropriate medical care, most patients can return home and their life expectancy is several decades. Opposite to the beliefs of many healthy individuals, LIS patients self-report a meaningful quality of life and the demand of euthanasia is uncommon (ALIS database and Doble et al., 2003). Even if good recovery of motor and speech function is very rare in LIS, recent studies show that intensive and early rehabilitation can improve functional motor outcome and verbal communication (Casanova et al., 2003; Pantke, 2005). Improvements in augmentative communication devices such as infrared eye-gaze sensors and switching devices, sometimes using minuscule electromyographic or even electroencephalographic signals (see Kubler et al, this volume), coupled to sophisticated computer translation software now give LIS patients a synthesized ''voice'' and enable them to control their surroundings in ways never possible before. New technology offer the LIS a virtual window on the world via internet and has permitted locked-in patients to resume an active role in society. Caring for LIS patients is far from futile.

Acknowledgments

This research was supported by the French Association Locked in Syndrome (ALIS), the Belgian Fonds National de la Recherche Scientifique (FNRS), the Centre Hospitalier Universitaire Sart Tilman, Liège, the University of Liège, the Erasme Hospital, University of Brussels, Belgium, and the Mind Science Foundation, San Antonio, Texas, USA. Steven Laureys is Research Associate at FNRS. The authors thank all participating LIS patients, their families, and their physicians and acknowledge Véronique Blandin and Dominique Toussaint for managing the ALIS database.

References

Acharya, V.Z., Talwar, D. and Elliott, S.P. (2001) Enteroviral encephalitis leading to a locked-in state. J. Child Neurol., 16: 864–866.

Allain, P., Joseph, P.A., Isambert, J.L., Le Gall, D. and Emile, J. (1998) Cognitive functions in chronic locked-in syndrome: a report of two cases. Cortex, 34: 629–634.

Allen, C.M. (1993) Conscious but paralysed: releasing the locked-in. Lancet, 342: 130–131.

American Congress of Rehabilitation Medicine (1995) Recommendations for use of uniform nomenclature pertinent to patients with severe alterations of consciousness. Arch. Phys. Med. Rehabil., 76: 205–209.

Anderson, C., Dillon, C. and Burns, R. (1993) Life-sustaining treatment and locked-in syndrome. Lancet, 342: 867–868.

Anonymous. (1973) Awareness during anaesthesia. Lancet, 2: 1305.

Bach, J.R. (2003) Threats to ''informed'' advance directives for the severely physically challenged? Arch. Phys. Med. Rehabil., 84: S23–S28.

Bakshi, N., Maselli, R.A., Gospe Jr., S.M., Ellis, W.G., McDonald, C. and Mandler, R.N. (1997) Fulminant demyelinating neuropathy mimicking cerebral death. Muscle Nerve, 20: 1595–1597.

Bassetti, C., Mathis, J. and Hess, C.W. (1994) Multimodal electrophysiological studies including motor evoked potentials in patients with locked-in syndrome: report of six patients. J. Neurol. Neurosurg. Psychiatry, 57: 1403–1406.

Batavia, A.I. (1997) Disability and physician-assisted suicide. N. Engl. J. Med., 336: 1671–1673.

Bauby, J.-D. (1997). The Diving Bell and the Butterfly (original title: Le scaphandre et le papillon, Robert Laffont, Paris) KNOPF, New York.

Bauer, G., Gerstenbrand, F. and Rumpl, E. (1979) Varieties of the locked-in syndrome. J. Neurol., 221: 77–91.

Bernat, J.L., Cranford, R.E., Kittredge Jr., F.I. and Rosenberg, R.N. (1993) Competent patients with advanced states of permanent paralysis have the right to forgo life-sustaining therapy. Neurology, 43: 224–225.

Breen, P. and Hannon, V. (2004) Locked-in syndrome: a catastrophic complication after surgery. Br. J. Anaesth., 92: 286–288.

Brighouse, D. and Norman, J. (1992) To wake in fright. BMJ., 304: 1327–1328.

Britt, R.H., Herrick, M.K. and Hamilton, R.D. (1977) Traumatic locked-in syndrome. Ann. Neurol., 1: 590–592.

Calder, A.J., Lawrence, A.D. and Young, A.W. (2001) Neuropsychology of fear and loathing. Nat. Rev. Neurosci., 2: 352–363.

Cappa, S.F., Pirovano, C. and Vignolo, L.A. (1985) Chronic 'locked-in' syndrome: psychological study of a case. Eur. Neurol., 24: 107–111.

Cappa, S.F. and Vignolo, L.A. (1982) Locked-in syndrome for 12 years with preserved intelligence. Ann. Neurol., 11: 545.

Carroll, W.M. and Mastaglia, F.L. (1979) 'Locked-in co ma' in postinfective polyneuropathy. Arch. Neurol., 36: 46–47.

Casanova, E., Lazzari, R.E., Lotta, S. and Mazzucchi, A. (2003) Locked-in syndrome: improvement in the prognosis after an early intensive multidisciplinary rehabilitation. Arch. Phys. Med. Rehabil., 84: 862–867.

Chang, B. and Morariu, M.A. (1979) Transient traumatic "locked-in" syndrome. Eur. Neurol., 18: 391–394.

Cherington, M., Stears, J. and Hodges, J. (1976) Locked-in syndrome caused by a tumor. Neurology, 26: 180–182.

Chia, L.G. (1991) Locked-in syndrome with bilateral ventral midbrain infarcts. Neurology, 41: 445–446.

Christakis, N.A. and Asch, D.A. (1993) Biases in how physicians choose to withdraw life support. Lancet, 342: 642–646.

Darolles, M. (1875) *Prog. Med.,* 3: 629.

Davis, L.E., Wesley, R.B., Juan, D. and Carpenter, C.C. (1972) "Locked-in syndrome" from diazepam toxicity in a patient with tetanus. Lancet, 1: 101.

Doble, J.E., Haig, A.J., Anderson, C. and Katz, R. (2003) Impairment, activity, participation, life satisfaction, and survival in persons with locked-in syndrome for over a decade: follow-up on a previously reported cohort. J. Head Trauma Rehabil., 18: 435–444.

Dumas, A. (1997) The Count of Monte Cristo. Wordworth Editions Limited, London.

Dunn, L. M. and Thériault-Whalen, C. M. (1993) Échelle de vocabulaire en images Peabody. American Guidance Service, Minnesota.

Durrani, Z. and Winnie, A.P. (1991) Brainstem toxicity with reversible locked-in syndrome after intrascalene brachial plexus block. Anesth. Analg., 72: 249–252.

Ebinger, G., Huyghens, L., Corne, L. and Aelbrecht, W. (1985) Reversible ''locked-in'' syndromes. Intensive Care Med., 11: 218–219.

Ethics and Humanities Subcommittee of the AAN (1993) Position statement: certain aspects of the care and management of profoundly and irreversibly paralyzed patients with retained consciousness and cognition. Report of the ethics and humanities subcommittee of the American academy of neurology. Neurology, 43: 222–223.

Feldman, M.H. (1971) Physiological observations in a chronic case of ''locked-in'' syndrome. Neurology, 21: 459–478.

Fitzgerald, L.F., Simpson, R.K. and Trask, T. (1997) Locked-in syndrome resulting from cervical spine gunshot wound. J. Trauma, 42: 147–149.

Fred, H.L. (1986) Helen. South Med. J., 79: 1135–1136.

Gallo, U.E. and Fontanarosa, P.B. (1989) Locked-in syndrome: report of a case. Am. J. Emerg. Med., 7: 581–583.

Ghorbel, S. (2002) Statut fonctionnel et qualité de vie chez le locked-in syndrome a domicile. In: DEA Motricité Humaine et Handicap, Laboratory of Biostatistics, Epidemiology and Clinical Research. Université Jean Monnet Saint-Etienne, Montpellier, France.

Golubovic, V., Muhvic, D. and Golubovic, S. (2004) Posttraumatic locked-in syndrome with an unusual three day delay in the appearance. Coll. Antropol., 28: 923–926.

Guerra, M.J. (1999) Euthanasia in Spain: the public debate after Ramon Sampedro's case. Bioethics, 13: 426–432.

Gutling, E., Isenmann, S. and Wichmann, W. (1996) Electrophysiology in the locked-in-syndrome. Neurology, 46: 1092–1101.

Haig, A.J., Katz, R.T. and Sahgal, V. (1986) Locked-in syndrome: a review. Curr Concepts Rehabil. Med., 3: 12–16.
Haig, A.J., Katz, R.T. and Sahgal, V. (1987) Mortality and complications of the locked-in syndrome. Arch. Phys. Med. Rehabil., 68: 24–27.
Hall, K.M., Knudsen, S.T., Wright, J., Charlifue, S.W., Graves, D.E. and Werner, P. (1999) Follow-up study of individuals with high tetraplegia (C1-C4) 14 to 24 years postinjury. Arch. Phys. Med. Rehabil., 80: 1507–1513.
Hawkes, C.H. and Bryan-Smyth, L. (1976) Locked-in syndrome caused by a tumor. Neurology, 26: 1185–1186.
Hayashi, H. and Kato, S. (1989) Total manifestations of amyotrophic lateral sclerosis. ALS in the totally locked-in state. J. Neurol. Sci., 93: 19–35.
Humbert, V. (2003) Je vous demande le droit de mourir. Michel Lafon, Paris.
Inci, S. and Ozgen, T. (2003) Locked-in syndrome due to metastatic pontomedullary tumor–case report. Neurol. Med. Chir. (Tokyo), 43: 497–500.
Jacome, D.E. and Morilla-Pastor, D. (1990) Unreactive EEG: pattern in locked-in syndrome. Clin. Electroencephalogr., 21: 31–36.
Katz, R.T., Haig, A.J., Clark, B.B. and DiPaola, R.J. (1992) Long-term survival, prognosis, and life-care planning for 29 patients with chronic locked-in syndrome. Arch. Phys. Med. Rehabil., 73: 403–408.
Keane, J.R. (1986) Locked-in syndrome after head and neck trauma. Neurology, 36: 80–82.
Kennedy, P.R. and Bakay, R.A. (1998) Restoration of neural output from a paralyzed patient by a direct brain connection. Neuroreport, 9: 1707–1711.
Kleinschmidt-DeMasters, B.K. and Yeh, M. (1992) ''Locked-in syndrome'' after intrathecal cytosine arabinoside therapy for malignant immunoblastic lymphoma. Cancer, 70: 2504–2507.
Kotchoubey, B., Lang, S., Winter, S. and Birbaumer, N. (2003) Cognitive processing in completely paralyzed patients with amyotrophic lateral sclerosis. Eur. J. Neurol., 10: 551–558.
Kubler, A., Winter, S., Ludoplh, A. C., Hautzinger, M. and Birbaumer, N. (2005) Depression and quality of life in ALS patients (submitted).
Landi, A., Fornezza, U., De Luca, G., Marchi, M. and Colombo, F. (1994) Brain stem and motor-evoked responses in ''locked-in'' syndrome. J. Neurosurg. Sci., 38: 123–127.
Landrieu, P., Fromentin, C., Tardieu, M., Menget, A. and Laget, P. (1984) Locked in syndrome with a favourable outcome. Eur. J. Pediatr., 142: 144–145.
Laureys, S., Owen, A.M. and Schiff, N.D. (2004a) Brain function in coma, vegetative state, and related disorders. Lancet Neurol., 3: 537–546.
Laureys, S., Perrin, F., Faymonville, M.E., Schnakers, C., Boly, M., Bartsch, V., Majerus, S., Moonen, G. and Maquet, P. (2004b) Cerebral processing in the minimally conscious state. Neurology, 14: 916–918.
Laureys, S., van Eeckhout, P., Ferring, M., Faymonville, M., Mavroudakis, N., Berre, J., Van Bogaert, P., Pellas, F., Cornu, P., Luxen, A., Vincent, J. L., Moonen, G., Maquet, P. and Goldman, S. (2003) Brain function in acute and chronic locked-in syndrome. Presented at the 9th Annual Meeting of the Organisation for Human Brain Mapping (OHBM), June 18-22, 2003, NY, USA, NeuroImage CD ROM Volume 19, Issue 2, Supplement 1.
Leon-Carrion, J., van Eeckhout, P. and Dominguez-Morales Mdel, R. (2002a) The locked-in syndrome: a syndrome looking for a therapy. Brain Inj., 16: 555–569.
Leon-Carrion, J., van Eeckhout, P., Dominguez-Morales Mdel, R. and Perez-Santamaria, F.J. (2002b) The locked-in syndrome: a syndrome looking for a therapy. Brain Inj., 16: 571–582.
Leplege, A., Ecosse, E., Verdier, A. and Perneger, T.V. (1998) The French SF-36 Health Survey: translation, cultural adaptation and preliminary psychometric evaluation. J. Clin. Epidemiol., 51: 1013–1023.
Levy, D.E., Sidtis, J.J., Rottenberg, D.A., Jarden, J.O., Strother, S.C., Dhawan, V., Ginos, J.Z., Tramo, M.J., Evans, A.C. and Plum, F. (1987) Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. Ann. Neurol., 22: 673–682.
Lilje, C.G., Heinen, F., Laubenberger, J., Krug, I. and Brandis, M. (2002) Benign course of central pontine myelinolysis in a patient with anorexia nervosa. Pediatr. Neurol., 27: 132–135.
Loeb, C., Mancardi, G.L. and Tabaton, M. (1984) Locked-in syndrome in acute inflammatory polyradiculoneuropathy. Eur. Neurol., 23: 137–140.
Markand, O.N. (1976) Electroencephalogram in ''locked-in'' syndrome. Electroencephalogr. Clin. Neurophysiol., 40: 529–534.
McCusker, E.A., Rudick, R.A., Honch, G.W. and Griggs, R.C. (1982) Recovery from the ''locked-in'' syndrome. Arch. Neurol., 39: 145–147.
Meienberg, O., Mumenthaler, M. and Karbowski, K. (1979) Quadriparesis and nuclear oculomotor palsy with total bilateral ptosis mimicking coma: a mesencephalic ''locked-in syndrome''? Arch. Neurol., 36: 708–710.
Messert, B., Orrison, W.W., Hawkins, M.J. and Quaglieri, C.E. (1979) Central pontine myelinolysis. Considerations on etiology, diagnosis, and treatment. Neurology, 29: 147–160.
Mikhailidis, D.P., Hutton, R.A. and Dandona, P. (1985) ''Locked in'' syndrome following prolonged hypoglycemia. Diabetes Care, 8: 414.
Morlan, L., Rodriguez, E., Gonzalez, J., Jimene-Ortiz, C., Escartin, P. and Liano, H. (1990) Central pontine myelinolysis following correction of hyponatremia: MRI diagnosis. Eur. Neurol., 30: 149–152.
Murphy, M.J., Brenton, D.W., Aschenbrener, C.A. and Van Gilder, J.C. (1979) Locked-in syndrome caused by a solitary pontine abscess. J. Neurol. Neurosurg. Psychiatry., 42: 1062–1065.
Negreiros dos Anjos, M. (1984) ''Locked in'' syndrome following prolonged hypoglycemia. Diabetes Care, 7: 613.
New, P.W. and Thomas, S.J. (2005) Cognitive impairments in the locked-in syndrome: A case report. Arch. Phys. Med. Rehabil., 86: 338–343.

Oda, Y., Okada, Y., Nakanishi, I., Kajikawa, K., Kita, T., Hirose, G. and Kurachi, M. (1984) Central pontine myelinolysis with extrapontine lesions. Acta Pathol. Jpn., 34: 403–410.

O'Donnell, P.P. (1979) 'Locked-in syndrome' in postinfective polyneuropathy. Arch. Neurol., 36: 860.

Ohry, A. (1990) The locked-in syndrome and related states. Paraplegia., 28: 73–75.

Onofrj, M., Thomas, A., Paci, C., Scesi, M. and Tombari, R. (1997) Event-related potentials recorded in patients with locked-in syndrome. J. Neurol. Neurosurg. Psychiatry., 63: 759–764.

Pantke, K.-H. (2005) Bestimmung des Barthelindex aus Beginn und Länge der Rehabilitation nach einer Basilarithrombose, (submitted).

Patterson, J.R. and Grabois, M. (1986) Locked-in syndrome: a review of 139 cases. Stroke, 17: 758–764.

Pecket, P., Landau, Z. and Resnitzky, P. (1982) Reversible locked-in state in postinfective measles encephalitis. Arch. Neurol., 39: 672.

Peduto, V.A., Silvetti, L. and Piga, M. (1994) An anesthetized anesthesiologist tells his experience of waking up accidentally during the operation. Minerva Anestesiol., 60: 1–5.

Perrin, F., Garcia-Larrea, L., Mauguiere, F. and Bastuji, H. (1999) A differential brain response to the subject's own name persists during sleep. Clin. Neurophysiol., 110: 2153–2164.

Perrin, F., Schnakers, C., Faymonville, M. E., Degueldre, C., Bredart, S., Collette, F., Lamy, M., Goldman, S., Moonen, G., Luxen, A., Maquet, P. and Laureys, S. (2005) Evaluation of preserved linguistic processing in brain damaged patients, (submitted).

Plum, F. and Posner, J.B. (1983) The Diagnosis of Stupor and Coma. Davis, F.A., Philadelphia, PA.

Pogacar, S., Finelli, P.F. and Lee, H.Y. (1983) Locked-in syndrome caused by a metastasis. R I Med. J., 66: 147–150.

Rae-Grant, A.D., Lin, F., Yaeger, B.A., Barbour, P., Levitt, L.P., Castaldo, J.E. and Lester, M.C. (1989) Post traumatic extracranial vertebral artery dissection with locked-in syndrome: a case with MRI documentation and unusually favourable outcome. J. Neurol. Neurosurg. Psychiatry., 52: 1191–1193.

Ragazzoni, A., Grippo, A., Tozzi, F. and Zaccara, G. (2000) Event-related potentials in patients with total locked-in state due to fulminant Guillain-Barre syndrome. Int. J. Psychophysiol., 37: 99–109.

Richard, I., Pereon, Y., Guiheneu, P., Nogues, B., Perrouin-Verbe, B. and Mathe, J.F. (1995) Persistence of distal motor control in the locked in syndrome. Review of 11 patients. Paraplegia., 33: 640–646.

Sandin, R.H., Enlund, G., Samuelsson, P. and Lennmarken, C. (2000) Awareness during anaesthesia: a prospective case study. Lancet, 355: 707–711.

Schnakers, C., Majerus, S., Laureys, S., Van Eeckhout, P., Peigneux, P. and Goldman, S. (2005) Neuropsychological testing in chronic locked-in syndrome. Psyche, abstracts from the Eighth Conference of the Association for the Scientific Study of Consciousness (ASSC8), University of Antwerp, Belgium, 26–28 June 2004, pp. 11.

Sigalovsky, N. (2003) Awareness under general anesthesia. Aana. J., 71: 373–379.

Steffen, G.E. and Franklin, C. (1985) Who speaks for the patient with the locked-in syndrome? Hastings Cent. Rep., 15: 13–15.

Stumpf, S.E. (1986) A comment on ''Helen''. South Med. J., 79: 1057–1058.

Tavalaro, J. and Tayson, R. (1997) Look Up for Yes. Kodansha America Inc, New York, NY.

Thadani, V.M., Rimm, D.L., Urquhart, L., Fisher, L., Williamson, P.D., Enriquez, R., Kim, J.H. and Levy, L.L. (1991) 'Locked-in syndrome' for 27 years following a viral illness: clinical and pathologic findings. Neurology, 41: 498–500.

Towle, V.L., Maselli, R., Bernstein, L.P. and Spire, J.P. (1989) Electrophysiologic studies on locked-in patients: heterogeneity of findings. Electroencephalogr. Clin. Neurophysiol., 73: 419–426.

Trail, M., Nelson, N.D., Van, J.N., Appel, S.H. and Lai, E.C. (2003) A study comparing patients with amyotrophic lateral sclerosis and their caregivers on measures of quality of life, depression, and their attitudes toward treatment options. J. Neurol. Sci., 209: 79–85.

van Eeckhout, P. (1997) Le locked-in syndrom. Rééducation Orthophonique, 35: 123–135.

Vigand, P. (2002) Promenades Immobiles Le Livre de Poche, Paris.

Vigand, P. and Vigand, S. (2000) Only The Eyes Say Yes (original title: Putain de silence). Arcade Publishing, NY.

Ware, J.E., Snow, K.K. and Kosinski, M. (1993) SF-36 Health Survey Manual and Interpretation Guide. The Health Institute, New England Medical Center, Boston, MA.

Zola, E. (1979) Thérère Raquin. Gallimard, Paris.